MR Imaging Biomarkers of Cardiac Function and Rotational Mechanics in Boys with Duchenne Muscular Dystrophy

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Synopsis

Duchenne Muscular Dystrophy (DMD) severely impacts heart health. Decreasing LV ejection fraction (EF) is a late and highly variable outcome in this cohort. Earlier indicators of cardiac involvement would improve patient management and provide insight into the utility of emerging therapies. Boys with DMD (N=25) and healthy volunteers (N=8) underwent cardiac MRI exams including short-axis tagged images. EF, peak LV twist, and peak mid-wall circumferential strain (Ecc) were estimated. Ecc and twist were significantly reduced in patients (9.3±4.3° vs. 14.8°±3.6°, p<0.004) and (-15.8±5.8% vs. -18.5±3.2%, p<0.02). Whereas, EF was not significantly different between groups. ~50% of DMD patients with normal EF had reduced twist and Ecc. Reduced peak LV twist and mid-wall Ecc measured by MR tagging may be earlier and more sensitive indicators of cardiac involvement in boys with DMD.

Background

Duchenne Muscular Dystrophy (DMD) is a fatal genetic disorder affecting 1 in 3000 boys. DMD severely impacts heart health, which has prompted recent clinical trials to include cardiac MRI biomarkers as end-points. Ejection fraction (EF) has been shown to decline ~2%/year, but is a late outcome and highly variable. Identifying earlier indicators of cardiac disease in this cohort may allow for more effective patient treatment and earlier insight to the utility of emerging therapies. Recent reports have indicated that peak mid-wall circumferential strain (Ecc) and LV twist are reduced in boys with DMD compared to healthy volunteers2,3. This work further characterizes both peak mid-wall Ecc and LV twist in a cohort of boys with DMD compared with healthy volunteers. The objective was to determine if reductions in peak mid-wall Ecc and LV twist can more sensitively distinguish cardiac dysfunction in this cohort compared to EF.

Methods

Study Population: In this IRB-approved and HIPAA-compliant prospective study, boys with DMD (N=25, age=14±5 years) and healthy volunteers (N=8, age=17±5 years) underwent a cardiac MRI examination after receiving informed consent.

MRI Protocol: Subjects were imaged at either 1.5T or 3T (Siemens Avanto/Skyra) using: 2D CINE images (1.4x1.4x6mm, TE/TR=1.2/45.1 ms) and basal, mid, and apical LV short-axis tagged images (1.4x 1.4x8mm, TE/TR=2.12/24-48 ms, 11-31 phases, tag spacing=8mm). Five DMD patients received a follow-up examination 12±5 months after the initial scan.

Data Processing and Statistical Analysis: LV Ejection Fraction (EF) was quantified from CINE images (Qmass, Medis; Argus, Siemens; and Circle CVI, Circle Cardiovascular Imaging). Peak mid-wall Ecc and peak LV twist were estimated from tagged MR images (Diagnosoft, Myocardial Solutions). Normally distributed data were compared with a two-tailed t-test. Non-parametric data were compared with a Kruskal-Wallice test. A Holm-Sidak post hoc correction accounted for multiple comparisons. Effect size (Cohen’s d) was computed to determine the non-overlap of statistically significant results.

Results

Table 1 and Figure 1 summarize LV ejection fraction, peak mid-wall Ecc and LV twist in boys with DMD and healthy volunteers. There was no significant difference in EF between groups (62.5±8.3% vs. 63.2±3.3%, p=N.S.). A significant reduction in LV twist (9.3±4.3° vs. 14.8°±3.6°, p<0.004) was observed in boys with DMD compared to volunteers. Peak mid-wall Ecc (-15.8±5.8% vs. -18.5±3.2%, p<0.02) was significantly lower in magnitude. The effect sizes for Ecc and LV twist were 0.29 and 0.56, which corresponds to a 21% and a 33% non-overlap of patient and volunteer data respectively. Figures 2 and 3 plot LV Ejection Fraction (EF) with DMD patients were not precisely age matched, peak mid-wall Ecc is known to decrease with age, and twist remains relatively constant until middle age5. Further investigation in a larger, longitudinal cohort is warranted.

Discussion & Conclusion

This data suggests that patients with DMD exhibit decreases in LV twist and peak mid-wall Ecc that likely precede decreases in EF as only a single patient with DMD was found to have "low EF, normal Twist/Ecc." Hence, LV twist and peak mid-wall Ecc measured by MR tagging may be earlier and more sensitive indicators of cardiac dysfunction in boys with DMD. Patients with reduced EF also displayed reductions in LV twist and Ecc, but importantly, ~50% of patients with normal EF had low twist and peak mid-wall Ecc. Further, early results with a limited sample size suggest that patients that have reduced EF on a follow-up exam also exhibit reductions in twist and Ecc. LV twist has a larger effect size than Ecc, and consequently may be a more sensitive measure of early dysfunction. These results corroborate the strain reports of Hor et al. and twist results of Rehyan et al. While volunteers and DMD patients were not precisely age matched, peak mid-wall Ecc is known to decrease with age, and twist remains relatively constant until middle age5.
Acknowledgements
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References


Figures
Table 1. Rotational Mechanics and circumferential strain in N=25 boys with DMD and N=8 Normal Volunteers shown as median ± standard deviation. * denotes a statistically significant difference at a confidence level of p<.05 with post hoc correction for multiple comparisons.

Table 1:

<table>
<thead>
<tr>
<th>Rotational Mechanics</th>
<th>DMD Patients</th>
<th>Normal Volunteers</th>
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<tbody>
<tr>
<td>Global Ecc (%)</td>
<td>-15.6 ± 6.6</td>
<td>-16.6 ± 3.2</td>
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<tr>
<td>Twist (degrees)</td>
<td>9.3 ± 4.3</td>
<td>14.8 ± 3.0</td>
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<tr>
<td>LV Ejection Fraction (%)</td>
<td>62.0 ± 8.3</td>
<td>63.2 ± 2.3</td>
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Figure 1: (A) Ejection Fraction, (B) Peak mid-wall Ecc, and (C) LV Twist for boys with DMD and Healthy Volunteers. There is no significant difference between patients and volunteers for EF. There is a significant difference in peak mid-wall Ecc and LV twist. Peak mid-wall Ecc and LV twist may be effective indicators of early cardiac dysfunction in DMD prior to changes in EF.

Figure 2: Peak mid-wall (Ecc) plotted as a function of EF for healthy volunteers (orange) and boys with Duchenne's muscular dystrophy (blue). A. The “Normal EF, Low Ecc” quadrant contains boys with DMD who have early signs of cardiac dysfunction and accounts for 52% of the patient cohort. B. “Low EF, Low Ecc” identifies 12% of boys with DMD. C. “Low EF, Normal Ecc” identifies 4% of boys with DMD. D. “Normal EF, Normal Ecc” contains all the healthy volunteers and 32% of boys with DMD and limited cardiac involvement.
**Figure 3:** Peak Twist plotted as a function of EF for healthy volunteers (orange) and boys with Duchenne's muscular dystrophy (blue).  

**A.** The “Normal EF, Normal Twist” quadrant contains all the healthy volunteers and 36% of boys with DMD and limited cardiac involvement.  

**B.** “Low EF, Normal Ecc” identifies 4% of boys with DMD.  

**C.** “Low EF, Low Twist” identifies 12% of boys with DMD.  

**D.** The “Normal EF, Low Twist” quadrant contains boys with DMD who have early signs of cardiac dysfunction and accounts for 48% of the patient cohort.

<table>
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<tr>
<th>Table 2: Follow Up Examination</th>
<th>First Exam</th>
<th>Second Exam</th>
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<tbody>
<tr>
<td>Global Ecc (%)</td>
<td>-17.7 ± 4.2</td>
<td>-15.7 ± 4.3</td>
</tr>
<tr>
<td>Twist (degrees)</td>
<td>11.7 ± 7.0</td>
<td>11.1 ± 5.2</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>67 ± 5.0</td>
<td>56 ± 8.0</td>
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*Table 2:* Follow up exams for boys with DMD (N=5), 12±5 months after the initial examination. The data suggests that patients exhibit a reduction in peak mid-wall Ecc, twist, and EF between the two examinations.